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FLOOD, MICHELE C	
ART UNIT	**PAPER NUMBER**
1655	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/692,105	BRADLEY ET AL.	
	Examiner	Art Unit	
	Michele Flood	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-53* is/are pending in the application.

4a) Of the above claim(s) *25-53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/05;8/04;5/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election without traverse of Claims 1-24; and, the species election of "the claimed invention where plasminogen is cleaved in the presence of epsilon amino caproic acid (EACA) with soluble streptokinase, and where the plasmin is formulated using acetic acid, trehalose, and, if with salt, with sodium chloride", in the reply filed on October 17, 2006 is acknowledged.

The elected species was not found. Therefore, the claims were examined to the extent that the next species was found.

Claims 1-24 are under examination.

Specification

The use of the trademark SEPHAROSE ™ has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. It is suggested that each letter of the trademark be capitalized or include a proper trademark symbol, such as ™ or ®.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The metes and bounds of Claim 1 are rendered uncertain by the phrase "buffering the plasmin solution with a low pH, low buffering capacity agent to form reversibly inactive acidified plasmin" because the preamble recites "A method for purifying plasmin", while the resultant product of the claim designated process steps results not in the making of a purified plasmin, but a reversibly inactive acidified plasmin. The lack of clarity renders the claimed subject matter confusing because it is uncertain as to whether the buffering of the plasmin solution is a step necessary for purifying plasmin or a step necessary for the making of a reversibly inactive acidified plasmin. The lack of clarity renders the claimed subject matter very vague and confusing.

The term "low pH" in Claims 1, 18 and 19 is a relative term which renders the claim indefinite. The term "low pH" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. For instance, it is unclear as to how low a pH does Applicant considers a low pH to be or in comparison

to what other pH. For example, a pH of 7.8 is a low ph when related to a pH of 9.2. The lack of clarity renders the claim indefinite.

With regard to Claims 8-10 and 14, the claims are not set forth in terms of a positive statement; and, therefore, the metes and bounds of the claim limitations are uncertain. This rejection is made with particular regard to Claim 8, wherein Applicant directs the instantly claimed invention to "wherein the plasminogen is cleaved in the presence of at least one excipient that is an omega-amino acid"; as well as Claim 9, wherein Applicant directs the instantly claimed invention to "wherein the plasminogen is cleaved in the presence of at least one omega-amino acid selected from the group consisting of lysine, epsilon amino caproic acid, tranexamic , poly lysine, arginine, and combinations thereof" because it is uncertain as to the subject matter to which Applicant intends to seek patent protection. As presently drafted, the recitation of "wherein the plasminogen is cleaved in the presence of at least one omega-amino acid" could read on a process step for the making of plasminogen. For example, Trese et al. (A*, US 6,207,066) teaches a method for making a purified plasminogen, wherein the plasminogen is prepared from blood plasma by binding plasminogen to an activated affinity cartridge containing lysine and contacting the absorbent material with amino caproic acid; and, wherein the plasminogen is "cleaved" from the affinity cartridge, Please note that Trese further teaches "cleaving" (converting or activating) plasminogen in the presence of the plasminogen activator, streptokinase, to yield an active plasmin. The lack of clarity renders the claims vague and ambiguous.

Claim 15, line 2, recites the abbreviation "tPA". Abbreviations in the first instance of claims should be expanded upon with the abbreviation indicated in parentheses. The abbreviations can be used thereafter. Applicant can overcome the rejection by replacing "tPA" with tissue plasminogen activator.

Claim 17 is rendered vague and indefinite by the trademark term "SEPHAROSE". The relationship between a trademark and the product it identifies is often indefinite, uncertain, and arbitrary. The formula or characteristics of the product may change from time to time and yet it may continue to be sold under the same trademark. In patent specifications, every element or ingredient of the product should be set forth in positive, exact, intelligible language, so that there will be no uncertainty as to what is meant. Arbitrary trademarks which are liable to mean different things at the pleasure of manufacturers do not constitute such language. Ex Parte Kattwinkle, 12 USPQ 11 (Bd. App. 1931).

Claims 19 recites the limitation "derivative". One of ordinary skill in the art would not know how to interpret the metes and bounds of this limitation. A derivation of a chemical compound may be closely patterned after the subject chemical compound or may be loosely patterned after the subject chemical compound, such that it may bear no resemblance or form recognizable as the subject chemical compound which maybe chemically and/or biologically unrelated in function or form to the subject chemical compound.

With regard to Claim 19, the term "alanine" appears twice in line 4. Applicant may overcome the rejection by deleting one of the repeated terms to avoid redundancy.

All other cited claims depend directly or indirectly from rejected claims and are, therefore, also, rejected under U.S.C. 112, second paragraph for the reasons set forth above.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 8-15 and 18-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Robbins et al. (D24, Robbins, K C et al., The Journal of Biological Chemistry (1963), 238: 952-962. Purification of human plasminogen and plasmin by gel filtration on Sephadex and chromatography on Diethylaminoethyl-Sephadex.).

Applicant claims a method for purifying plasmin comprising: cleaving a plasminogen in the presence of a plasminogen activator to yield an active plasmin; substantially removing the plasminogen activator from the active plasmin by binding the active plasmin to an active plasmin-specific absorbent material to form a bound plasmin, and eluting the bound plasmin with an excipient solution having a pH from about 2.5 to about 9.0 to form a plasmin solution; and buffering the plasmin solution with a low pH, low buffering capacity agent to form a reversibly inactive acidified plasmin. Applicant further claims the method of claim 1, wherein the excipient solution has a pH from about 4.0 to about 7.5; wherein the excipient solution has a pH of about 6.0;

wherein the plasminogen is cleaved in the presence of at least one excipient that is an omega-amino acid; wherein the plasminogen is cleaved in the presence of at least one omega-amino acid selected from the group consisting of lysine, epsilon amino caproic acid, tranexamic , poly lysine, arginine, and combinations thereof; wherein the plasmin is eluted in a solution comprising at least one salt, the solution having a conductivity from about 5 mS to about 100 mS. Applicant further claims the method of claim 10, wherein the at least one salt is sodium chloride. Applicant further claims the method of claim 11, wherein the sodium chloride is present at a concentration of from about 50 mM to about 1000 mM; and, wherein the sodium chloride is present at a concentration of about 150 mM. Applicant further claims the method of claim 1, wherein the plasminogen is cleaved using a catalytic concentration of a plasminogen activator that is selected from the group consisting of immobilized plasminogen activators, soluble plasminogen activators, and combinations thereof; wherein the plasminogen activator is selected from the group consisting of streptokinase, urokinase, tPA, and combinations thereof; wherein the low pH low buffering capacity agent comprises a component selected from the group consisting of an amino acid, a derivative of at least one amino acid, an oligopeptide which includes at least one amino acid, and combinations thereof; and, wherein the low pH, low buffering capacity agent comprises a component selected from the group consisting of acetic acid, citric acid, hydrochloric acid, carboxylic acid, lactic acid, malic acid, tartaric acid, benzoic acid, serine, threonine, methionine, glutamine, alanine, glycine, isoleucine, valine, aspartic acid, derivatives thereof, and combinations thereof; wherein the buffer is present in the reversibly inactive acidified

plasmin at a concentration at which the pH of the acidified plasmin is raised to neutral pH by adding serum in an amount no more than 5 times the volume of the acidified plasmin; and, wherein the reversibly inactive acidified plasmin solution has a pH between about 2.5 to about 4. Applicant further claims the method of claim 1, further including stabilizing the reversibly inactive acidified plasmin by adding a stabilizing agent selected from the group consisting of a polyhydric alcohol, pharmaceutically acceptable carbohydrates, salts, glucosamine, thiamine, niacinamide, and combinations thereof. Applicant further claims the method of claim 22, wherein the salts are selected from the group consisting of sodium chloride, potassium chloride, magnesium chloride, calcium chloride and combinations thereof.

Robbins teaches a method for purifying plasmin comprising the instantly claimed process steps. For example, the plasmin taught by Robbins is prepared by activation of the proenzyme with trace quantities of urokinase in glycerol, and isolation in a high state of purity by chromatography on DEAE-Sephadex™ columns. On page 956, Column 1, line 22 to page 957, Column 2, line 9, Robbins teaches complete conversion of plasminogen to plasmin with trace quantities of urokinase in a system containing 25% glycerol, 0.01M phosphate, and 0.034 glycine at pH 7.4. After activation, the plasmin was precipitated at pH 6.2 ± 0.2 with NaH_2PO_4 and dissolved in 0.005 N HCl; and, dialyzed at pH 3.7 followed by drying from the frozen state is taught as an alternative method. Robbins also teaches a method for further purification of plasmin by chromatography on DEAE-Sephadex™. For example, after isoelectric precipitation, the urokinase-activated plasmin was dissolved in 0.05M Tris-0.02 M lysine-0.1M NaCl

buffer, pH 9.0, and dialyzed against 10 volumes of this buffer. Then, the enzyme was chromatographed on DEAE-Sephadex™. The pool was adjusted to pH 3.7 with N HCl and dried from the frozen state. The dried enzyme preparation was dissolved in a small volume of 50% glycerol. Robbins teaches, "The solution contained 73.3 units per ml and 3.7 mg of protein per ml." *See* page 956, Column 2, lines 54-55. On page 957, Column 1, lines 6-10, Robbins teaches, "Urokinase cannot be detected by enzymatic methods in any of the plasmin preparations." With regard to the claim limitation of "a reversibly inactive, acidified plasmin", Robbins teaches measuring plasmin activity of the referenced fibrinolytic composition using an adapted caseinolytic assay performed at a pH of 7.4, on page 952, Column 1, line 24 to Column 2, line 28; and, on page 962, Column 1, lines 40-42, Robbins teaches that the prepared plasmin had a specific activity of 21.4 casein units per mg of protein or 140 casein units per mg of nitrogen. Moreover, on page 958, Column 2, lines 1-3, Robbins expressly teaches a purified plasmin solution in a pH 2.9 glycine buffer. With particular regard to the claimed subject matter, on page 958, Column 2, lines 15-17, Robbins expressly teaches a purified plasmin (No. 47) in 0.001 N HCl containing 0.1 M NaCl, ph 2.8, at 20°, which appears to be one and the same fibrinolytic composition disclosed and instantly claimed by Appellant. With regard to the claim limitation of "wherein the composition is a solution suitable for pharmaceutical use that can be raised to physiological pH by adding no more than about 5 volumes of serum to the solution relative to the volume of solution", as set forth in independent Claims 1 and 20, the Office finds that the fibrinolytic composition taught by Robbins is a solution suitable for pharmaceutical use, since there

is nothing contained therein the Robbins' composition to preclude pharmaceutical use thereof the referenced composition, that can be raised to physiological pH by adding no more than about 5 volumes of serum to the solution relative to the volume of solution, as evidenced by the following calculations set forth in the table and assumptions presented below, which are based on the teachings set forth in the following website article: http://www.lakesidepress.com/pulmonary/books/physiology/chap7_1.htm, Chapter 7: Acid-Base Balance.

1. Serum is plasma with the fibrinogen removed by precipitation. Plasma is blood with the cells removed. Hence, serum is blood with both cells and fibrinogen removed. Accordingly, serum will be treated as if it was blood for the pH calculations. The only buffer of significance in blood is H2C03.
2. The article (http://www.lakesidepress.com/pulmonary/books/physiology/chap7_1.htm, Chapter 7: Acid-Base Balance) gives the normal physiological pH range as 7.3-7.52. It is reasonably assumed that the serum starts at a physiological pH and ends in a physiological pH as required by the claims. This sets the upper and lower bounds for the pH start and finish as these values.
3. The Office used the Henderson-Hasselbach equation, Eqn 7-2, to calculate the [HCO3] at each pH assuming that the blood gas remained constant at 40 torr (reasonable since the dilution is rapid).

4. Assuming that all of the plasmin to be titrated is in the acid form to start with and assuming that all of it is fully titrated by the serum, the change in [HCO3] is how much is titrated.
5. For convenience of calculation, the Office chose the volume of serum to be 1.0 liter, and the maximum volume of the plasmin to be titrated to be 0.2 L.
6. Therefore V1*M1=V2*M2, V1=1, V2=0.2, thus M1/V2=M2, the concentration of the buffer to be titrated. Our calculations show the maximum concentration of the buffer to be titrated at different starting pH values for the serum, as presented in the table below.

pH	$[H^+]$ nM	pCO2 torr	[HCO3] mEq/L	Change mEq/L	[.2V Plasmin] mEq/L
7.3	50	40	19.0	0.0	0.0
7.35	45	40	21.3	2.3	11.6
7.4	40	40	23.9	4.9	24.6
7.45	35	40	26.9	7.8	39.2
7.52	30	40	31.6	12.5	62.7

Thus, the range of concentration for the plasmin acid that can be titrated with no more than five volumes of serum and maintain the pH in physiological values is in the range of 0.0-62.7 mEq/L.

Now, we look to the teachings of Robbins et al. (1963). Acidified plasmin (No. 47) in 0.001 N HCl, ~pH of 2.8, is used in the sedimentation analysis at page 958, column 2, last paragraph. This is equal to 1 mEq of acid and hence, well with the range of plasmin acid that can be titrated, unless the initial pH of the serum is at the lower bound of 7.3. Even at a slightly higher pH value of 7.35, the serum has sufficient capacity to neutralize the amount of acid in the acidified plasmin taught by Robbins.

The reference anticipates the claimed subject matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4 and 8-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robbins et al. (D24) in view of Sherry (D25, Sherry, S. J. Amer. Coll. Cardiol. (1989). The origin of thrombolytic therapy.), Castellino et al. (D9, Castellino, FJ et al. Meth. Enzymology (1981), 80: 365-378. Human plasminogen.), Morii et al. (N, EP

0256836 A1) and Wiman (D27, Wiman, B. Biochem. J. (1980), 191(1): 229-232. Affinity-chromatographic purification of human alpha 2-antiplasmin.).

Applicant's claimed invention of 1-3, 8-15 and 18-23 was set forth above. Applicant further claims the method of claim 1, wherein the plasminogen activation is soluble streptokinase; and, wherein the plasminogen activator is immobilized on a solid support medium comprising SEPHAROSE™.

The teachings of Robbins are set forth above. Robbins does not teach a method for purifying plasmin wherein the plasminogen activator is either streptokinase or tPA; wherein the plasminogen is soluble streptokinase; and, wherein the plasminogen activator is immobilized on a solid support medium comprising SEPHAROSE™. However, it would have been obvious to one of ordinary skill in the art to modify Robbins' method of making plasmin by adding and/or replacing the process steps and/or ingredients to provide the claimed invention because at the time the invention was made it was known in the art that the instantly claimed process steps and ingredients were beneficial in the making of plasmin, as evidenced by the teachings of Sherry, Castellino, Morii and Wiman. Firstly, both Sherry and Castellino, like Robbins, teach that streptokinase can activate plasminogen to plasmin. Moreover, on page 1091, Column 1, lines 29-33, Sherry teaches recombinant tPA as a plasminogen activator. Secondly, Morii teaches tissue plasminogen activator (tPA) as a plasminogen activator. Thirdly, Wiman teaches a method for purifying plasminogen to plasmin comprising activation of plasminogen to plasmin with SEPHAROSE™ -bound urokinase, on page 229, lines 29-31. At the time the invention was made, one of

ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to modify Robbins' method of making plasmin by adding and/or replacing the process steps and/or ingredients to provide the claimed invention because Sherry teaches that the knowledge of streptokinase as an plasminogen activator to yield plasmin is well established in the history of thrombolytic therapy; with regard to streptokinase, Castellino teaches, "Once formed, the activator complex activates human plasminogen in a similar fashion to urokinase", on page 1091, Column 1, lines15-17; Robbins teaches, "High purity plasmin can be prepared from Kline method plasminogen by activation with streptokinase, on page 952, Column 1, lines 7-9; Morii teaches that tPA made by his method is free of impurities and the activity of the tPA is unchanged; and, finally, the method of purifying plasminogen with SEPHAROSE™-bound urokinase taught by Wiman would have provided a one step method for the activation and purification of plasminogen to plasmin by modifying the Robbins' method, which would save time and reduce production cost of the composition.

Moreover, it would have been obvious to one of ordinary skill in the art at the time the invention was made to add the claimed ingredient in the making of the claimed composition and method because it is well known that its *prima facie* obvious to combine two or more ingredients each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is useful for the same purpose. The idea for combining them flows logically from their having been used individually in the prior art. *In re Pinten,* 459 F. 2d 1053, 173 USPQ 801 (CCPA 1972);

In re Susi, 58 CCPA 1074, 1079-80; 440 F.2d 442, 445; 169 USPQ 423, 426 (1971); *In re Crockett,* 47 CCPA 1018, 1020-21; 279 F.2d 274, 276-277; 126 USPQ 186, 188 (1960). Thus, at the time the invention was made, one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to replace one ingredient for the other because the claimed invention is no more than the substitution of known ingredients, one for the other, which have the same functional effect for the purification of a plasmin from plasminogen; and the claimed process step is no more than the replacement of a two-step process with a one-step process step. Thus, the claim limitations are no more than an arbitrary matter of experimental design choice to result the purification of a product.

Accordingly, the claimed invention was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

Claims 1-5 and 8-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robbins et al. (D24), Sherry (D25, Sherry, S. J. Amer. Coll. Cardiol. (1989). The origin of thrombolytic therapy.), Castellino et al. (D9, Castellino, FJ et al. Meth. Enzymology (1981), 80: 365-378. Human plasminogen.), Morii et al. (N, EP 0256836 A1) and Wiman (D27, Wiman, B. Biochem J. (1980), 191(1): 229-232. Affinity-chromatographic purification of human alpha 2-antiplasmin.) in view of Silver et al. (P1, IS 6,479,253 B1), Yago et al. (P3, US 5,879,923) and Diedrichsen et al. (P18, US 4,462,980).

Applicant's invention of Claims 1-4 and 8-23 was set forth above. Applicant further claims the method of claim 1, wherein the active plasmin-specific absorbent material comprises benzamidine; wherein the plasminogen activator is further removed by hydrophobic interaction; and, further including stabilizing the reversibly inactive acidified plasmin by adding a sugar or sugar alcohol selected from the group consisting of glucose, maltose, mannitol, sorbitol, sucrose, lactose, trehalose, and combinations thereof.

The combined teachings of Robbins, Sherry, Castellino, Morii and Wiman are set forth above. The combined teachings as set forth immediately above teach the claimed method except for the instantly claimed ingredients. However, it would have been obvious to one of ordinary skill in the art to add the instantly claimed ingredients to the modified method for purifying plasmin taught by the combined teachings of Robbins, Sherry, Castellino, Morii and Wiman to provide the claimed invention because at the time the invention was made it was known in the art that the instantly claimed process ingredients were beneficial in the purification of plasmin composition, as evidenced by the teachings Silver, Yago and Diedrichsen. Firstly, Silver teaches a method of purifying a serine protease (note that plasmin is a serine protease) comprising binding the serine protease to a column comprising p-aminobenzamidine crosslinked to SEPHAROSE™ beads, in Column 30, lines 29-42. In Column 22, lines 35-42, Silver also teaches that purification of proteins, such as the serine proteases, by affinity chromatography, ion exchange chromatography, filtration chromatography, hydrophobic interaction chromatography, gel filtration chromatography, *etc.*, are standard protein

purification techniques. Secondly, Yago teaches compositions comprising plasmin and the following (B-1): an oligopeptide comprising at least two amino acids bonded to each other, where the two amino acids are selected from the group consisting of lysine, arginine, glycine, alanine, aspartic acid and methionine; (B-2): at least two amino acids selected from the group consisting of lysine, arginine, glycine, alanine, aspartic acid and methionine; or (B-3): an amino acid selected from the group consisting of lysine, arginine, glycine, alanine, aspartic acid and methionine and a polyhydric alcohol. Yago teaches that the combining of plasmin with any of the components of either (B-1), (B-2) or (B-3) stabilizes the activity of plasmin. Thirdly, in Column 2, line 62 to Column 3, lines 33, Diedrichsen teaches stabilizing plasmin compositions with polyhydroxy compounds, such as sugars and sugar alcohols, as well as glycerol. For example, in Column 7 under "Example 1", Diedrichsen teaches a method of making a stable solid formulation of active plasmin wherein the pH is adjusted to 3.0 Diedrichsen also teaches a method of admixing the plasmin preparations with labeled glucose technetium-99m at pH 2.0-4.0. *See* Column 6, lines 14-19. At the time the invention was made, one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to modify the method of making the composition taught by the combined teachings Robbins, Sherry, Castellino, Morii and Wiman by adding the instantly claimed ingredients to provide the claimed invention because Silver teaches that the purification of serine proteases, such as plasmin, by benzamidine comprising absorbent material and hydrophobic interaction chromatography is well-established and well-known; Yago teaches that plasmin comprising plasmin in

combination with an additional component, such as, 1) an oligopeptide comprising at least two amino acids, or 2) at least two amino acids, or 3) a single amino acid and a polyhydric alcohol provides a stable plasmin for a long time; and, finally, Diedrichsen teaches adding polyhydric compounds, such as sugars and sugar alcohols, and glycerol to acidified plasmin compositions as stabilizing agents to impede the aggregation of plasmin and thus the denaturation of the composition thereof.

Moreover, it would have been obvious to one of ordinary skill in the art at the time the invention was made to add the claimed ingredients in the method of making the claimed composition because it is well known that its *prima facie* obvious to combine two or more ingredients each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is useful for the same purpose. The idea for combining them flows logically from their having been used individually in the prior art. *In re Pinten,* 459 F. 2d 1053, 173 USPQ 801 (CCPA 1972); *In re Susi,* 58 CCPA 1074, 1079-80; 440 F.2d 442, 445; 169 USPQ 423, 426 (1971); *In re Crockett,* 47 CCPA 1018, 1020-21; 279 F.2d 274, 276-277; 126 USPQ 186, 188 (1960).

Accordingly, the claimed invention was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

Claims 1-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robbins et al. (D24), Sherry (D25, Sherry, S. J. Amer. Coll. Cardiol. (1989). The origin of thrombolytic therapy.), Castellino et al. (D9, Castellino, FJ et al. Meth. Enzymology

(1981), 80: 365-378. Human plasminogen.), Morii et al. (N, EP 0256836 A1) and Wiman (D27, Wiman, B. Biochem J. (1980), 191(1): 229-232. Affinity-chromatographic purification of human alpha 2-antiplasmin.), Silver et al. (P1, IS 6,479,253 B1), Yago et al. (P3, US 5,879,923) and Diedrichsen et al. (P18, US 4,462,980) in view of Trese et al. (A) and Hiemstra et al. (N).

Applicant's claimed invention of Claims 1-5 and 8-24 was set forth above. Applicant further claims the method of Claim 1, further comprising nanofiltration of the plasmin solution. Applicant further claims the method of Claim 6, wherein the nanofiltration is carried out using a filter membrane characterized by an average pore size of approximately 15 nm.

The combined teachings of Robbins, Sherry, Castellino, Morii, Wiman, Silver, Yago and Diedrichsen are set forth above. The combined teachings as set forth immediately above teach the claimed method except for the instantly claimed process step. However, it would have been obvious to one of ordinary skill in the art to add the instantly claimed process step to the modified method for purifying plasmin taught by the combined teachings of Robbins, Sherry, Castellino, Morii, Wiman, Silver, Yago and Diedrichsen to provide the instantly claimed invention because at the time the invention was made it was known in the art that the instantly claimed process step was beneficial in the purification of a plasmin composition, as evidenced by the teachings of Trese and Hiemstra. Firstly, Trese teaches a method for making a purified plasminogen from blood plasma comprising binding plasminogen to an activated affinity cartridge containing lysine, contacting the absorbent material with an elution buffer containing

episilon-aminocaproic acid, and releasing the bound plasminogen from the affinity cartridge by injecting an elution buffer containing episilon-aminocaproic acid into the affinity cartridge. Trese further teaches cleaving the purified plasminogen in the presence of streptokinase to yield an active plasmin and further subjecting the plasmin to nanofiltration, wherein the nanofiltration is carried out using a filter membrane having an average pore size of 10 to about 30 nm, preferably 15 nm. Secondly Hiemstra teaches a method for removing viruses from a protein solution comprising subjecting the solution to a prefiltration step to remove large proteins and subjecting the resulting product to nanofiltration which removes viruses. On page 5, lines 11-21, Hiemstra further teaches that the prefiltration step removes high molecular weight contaminants, such as fibrinogen, from a blood derived protein solution; and, on page 4, lines 22-27, Hiemstra teaches that the step of nanofiltration is carried out over a nanofilter having a cut-off value of between about 10 to about 30 nm, preferably 15 nm to remove disease-causing viruses. At the time the invention was made, one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to add a further process step comprising nanofiltration of the plasmin solution taught by the combined teachings of the aforementioned references to provide the instantly claimed invention because both Trese and Hiemstra taught that nanofiltration of blood derived products removed disease causing viruses from blood products and provided a blood-derived product that is safe for human administration for therapeutic purposes. Thus, the claim limitations are no more than an arbitrary matter of

experimental design choice to provide a result effect variable for the purification of a product.

Accordingly, the claimed invention was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

Claims 1-3, 5-15 and 18-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robbins et al. (D24) in view of Silver et al. (P1, IS 6,479,253 B1), Trese et al. (A*), Hiemstra et al. (N) and Diedrichsen et al. (P18, US 4,462,980).

Applicant's claimed invention was set forth above.

The teachings of Robbins are set forth above. Robbins teaches the instantly claimed invention except for wherein the plasminogen is further removed by hydrophobic interaction; wherein the plasminogen is further removed by hydrophobic interaction; further comprising nanofiltration of the plasmin solution wherein the nanofiltration is carried out using a filter membrane characterized by an average pore size of approximately 15 nm; and, further including stabilizing the reversibly inactive acidified plasmin by adding a sugar or sugar alcohol selected from the group consisting of glucose, maltose, mannitol, sorbitol, sucrose, lactose, trehalose, and combinations thereof. However, it would have been obvious to one of ordinary skill in the art to add the instantly claimed process steps and ingredients to the method of purifying a plasmin taught by Robbins by adding the claim designated limitations because at the time the invention was made the instantly claimed process steps and ingredients were known in

the art to be beneficial in the making of a purified plasmin, as evidenced by the teachings of Silver, Trese, Hiemstra and Diedrichsen set forth herein. One of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to add the instantly claimed process steps and ingredients to the method of purifying a plasmin taught by Robbins to provide the instantly claimed method because at the time the invention was made Silver taught a method of purifying a serine protease (note that plasmin is a serine protease) comprising binding the serine protease to a column comprising p-aminobenzamidine crosslinked to SEPHAROSE™ beads, in Column 30, lines 29-42; and, in Column 22, lines 35-42, Silver also teaches that purification of proteins, such as the serine proteases, by affinity chromatography, ion exchange chromatography, filtration chromatography, hydrophobic interaction chromatography, gel filtration chromatography, *etc.*, are standard protein purification techniques; both Trese and Hiemstra taught that nanofiltration of blood derived products removed disease causing viruses from blood products and provided a blood-derived product that is safe for human administration for therapeutic purposes, wherein the nanofiltration was carried out using a filter membrane filter characterized by an average pore size of approximately 15 nm; and, Diedrichsen taught that the addition of polyhydric compounds, such as sugars and sugar alcohols, and glycerol to acidified plasmin compositions stabilize the acidified plasmin product and impedes aggregation of the plasmin composition; and, thus the denaturation of the composition. Thus, the claim limitations would have been no more than an arbitrary matter of experimental design choice to one of ordinary skill in the art practicing the invention at the time the

invention was made to provide a result effect variable for the purification of a product, especially given the beneficial teachings of the prior before him or her.

Accordingly, the claimed invention was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-5, 8, 14-16 and 18-24 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 1-8, 10, 11 and 13-20 of copending Application No. 10/143,156. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are no more than obvious variants of one another.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michele Flood whose telephone number is 571-272-0964. The examiner can normally be reached on 7:00 am - 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Terry McKelvey can be reached on 571-272-0775. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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